Editorial

Targeting HSP90 in malignant gliomas: onalespib as a potential therapeutic

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Glioblastoma (GBM) is the most common of all high-grade gliomas (HGGs). It accounts for almost 80% of all malignant primary neoplasms of the brain (1). It is a very aggressive tumor, with historical median survival rates of less than 2 years. Patients receiving standard of care following surgical resection, temozolomide (TMZ) plus radiation therapy, have a median survival of 14-18 months, highlighting the need for developing novel therapeutic strategies to effectively target malignant gliomas while preserving quality of life (2). Malignant gliomas are characterized by cellular heterogeneity, are highly vascularized, and invasive, which influence their resistance to conventional treatments and poor clinical outcomes. In addition, glioma stem-like cells (GSCs) contribute to the aggressive nature and incidence of malignant glioma recurrence (3). GSCs drive tumor initiation and proliferation, and are resistant to radiation and classical chemotherapeutic agents such as TMZ (4,5).

Despite significant efforts, advances in developing more effective therapies for malignant gliomas have been slow. In the past thirteen years, only three therapies have been approved by the FDA for GBM—TMZ, bevacizumab, and tumor-treating fields (TTF). In order to be effective, novel therapeutic candidates for malignant glioma must overcome several challenges: (I) they must have good blood-brain barrier penetrance; (II) kill GSCs; (III) synergize with radiation therapy and/or TMZ; (IV) block multiple critical pathways to impede GBM growth and survival; while (V) sparing normal brain tissue and minimizing toxicity.

Heat shock proteins (HSPs) are an evolutionarily conserved class of molecular chaperones that are involved in protein folding, intracellular availability, and proteolytic turnover of many key regulators of cell growth and survival. Among them, HSP90 has gained particular interest as a potential therapeutic target in cancer as it is overexpressed in various solid and hematologic malignancies (6,7). HSP90 can regulate the conformation and stability of many client proteins including signaling protein kinases (e.g., EGFR, MAPK cascades, Akt kinase), and steroid hormone receptors, many of which are deregulated in GBM (8). Currently, there are five HSP90 inhibitors undergoing interventional trials in multiple cancer indications, although none in GBM to date (9,10). Preclinical studies of HSP90 inhibitors 17-AAG and analogues in malignant glioma have demonstrated potent efficacy alone or in combination with conventional therapeutics although clinical development has been hindered (9,11,12).

In a recent report published in *Clinical Cancer Research*, Canella and colleagues evaluate the efficacy of onalespib, a second generation HSP90 inhibitor, as a single agent and in combination with TMZ against malignant gliomas including patient-derived GSCs *in vitro*, and in two distinct glioma xenograft models using zebrafish and NOD/SCID mice. Onalespib inhibited proliferation, survival, angiogenic potential, and migration of human glioma cell lines. Onalespib inhibited the EGFR signaling pathway and downstream signaling intermediaries AKT, ERK1/2, and S6 in human glioma cell lines and GSCs. Notably, onalespib depleted mutant EGFRvIII and its downstream intermediates in glioma cell lines. EGFRvIII is the most common gain-of function EGFR mutation in GBM and is known to enhance tumorigenicity (13). Further, they

examined the efficacy of onalespib against the mesenchymal (MES) and proneural (PN) GSC subtypes, and found that HSP90 inhibition decreased survival, invasion, and inhibited phosphorylation of STAT3.

Pharmacokinetics in non-tumor-bearing nude mice revealed the concentration of onalespib in the brain surpassed the plasma concentration two hours post-intravenous administration, which indicated that onalespib can cross the intact blood brain barrier. Immunohistological analysis of brain tissue of onalespib-treated mice revealed a time-dependent increase in HSP70 expression, which further validated onalespib's potent ability to inhibit HSP90 in the brain.

Lastly, they examined whether onalespib and TMZ exerted synergistic activity, and found this combination had synergistic or additive activity in glioma cells. In an orthotopic intracranial zebrafish glioma model, onalespib plus TMZ reduced tumor burden and extended survival compared to either individual treatment alone. To examine the effect of onalespib in a more clinically relevant model, they evaluated the effect of this combination therapy in NOD/SCID mouse xenograft model implanted with an aggressive patient-derived GSC line. The results were encouraging, this combination treatment significantly improved survival compared to vehicle or single agent treatment. Furthermore, examining the effect of the onalespib plus TMZ combination on survival and tumor burden against the MES GBM subtype in xenograft models could further strengthen the argument that the anti-tumor activity of onalespib is not restricted to certain GBM subtypes.

This study demonstrates the superior pharmacodynamics of this second generation HSP90 inhibitor compared to older HSP90 inhibitors in glioma models, which have been hindered by their low BBB penetrance, limited target inhibition, and toxicities (14). However, more questions must be addressed before onalespib can be examined clinically as a glioma treatment. Degradation of HSP90 clients is mediated by the proteasome (15). Does onalespib, through accumulation of misfolded client proteins, enhance proteasomal stress? Examination of whether the combination onalespib plus marizomib, a potent brain-penetrant proteasomal inhibitor, exhibits synergistic activity *in vitro* and *in vivo* is of great interest (16,17). Previous studies have reported enhanced HSP90 inhibition in 17-AAG in combination with bortezomib in multiple myeloma, likely due to an increase in protein misfolding and impaired protein degradation by the ubiquitin-proteasome pathway (18). Additionally, as TMZ plus radiation therapy is the standard of care for glioma, examining the effect of onalespib in combination with TMZ and radiation therapy in pre-clinical models is needed. DNA repair enzyme gene O^6-Methylguanine-DNA methyltransferase (MGMT) promoter methylation is associated with enhanced overall survival and sensitivity to TMZ (19). To determine which patients may potentially benefit from onalespib, newly diagnosed and/or patients with recurrent glioma; examining the effect of onalespib on TMZ resistant glioma lines and xenograft models is needed. Determining whether onalespib can sensitize TMZ resistant gliomas to TMZ or other drug combinations is of utmost importance.

As long-term survivorship in glioma patients is increasing, the quality of life of survivors should be preserved by using novel treatments that demonstrate potent activity against aggressive GSCs and glioma cells, while exhibiting minimal neurotoxicity. Previous studies have shown that NSCs have low HSP90 constitutive expression suggesting that HSP90 inhibitors might selectively target GSCs while not depleting NSCs (11,12). Exposing neural stem/cell progenitor cells to graded doses of onalespib, evaluating survival, HSP90 inhibition, and differentiation potential shall shed light on onalespib-related neurotoxicity.

Onalespib is currently being evaluated in several clinical trials for various malignancies, including advanced solid tumors and metastatic gastrointestinal stromal tumors (20,21); however, this is the first preclinical study to examine the effect of onalespib in glioma. Canella *et al.* elegantly demonstrates the potent effect of onalespib against gliomas in *in vitro* and *in vivo* models, as a single-agent, and in combination with TMZ, further supporting HSP90 inhibition as therapeutic strategy for GBM.

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Footnote

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